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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/621,269	THORPE ET AL.	
	Examiner	Art Unit	
	LAURA B. GODDARD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,14,18,23,51,52,94,96-99,106,107,112,117 and 122-149* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *107,130,131,148 and 149* is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☒ Claim(s) *134, 138, and 144* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims rejected are 1,14,18,23,51,52,94,96-99,106,112,117,122-129,132,133,135-137,139-143 and 145-147.

DETAILED ACTION

1. The Amendment filed April 11, 2008 in response to the Office Action of October 9, 2007, is acknowledged and has been entered. Claims 1, 14, 18, 23, 51, 52, 94, 96-99, 106, 107, 112, 117, and 122-149 are pending and currently being examined. Claims 2-13, 15-17, 19-22, 24-50, 53-93, 95, 100-105, 108-111, 113-116, 118-121 are canceled. Claims 123- 149 are new. Previously pending claims 1, 14, 18, 23, 94, 96-99, and 107 have been amended.

Claim Objections

2. Claims 134, 138, and 144 are free of the art but are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

New Rejection

(based on new considerations)

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 106, 112, 117, and 122-129 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in

such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not provide evidence that the claimed biological materials are known and readily available to the public.

The invention appears to employ novel biological materials, specifically antibody 3G4 produced from hybridoma ATCC PTA 4545. Exact replication of a cell line is an unpredictable event. Although applicant has provided a written description of a method for selecting the claimed hybridoma cell lines and monoclonal antibodies, this method will not necessarily reproduce antibodies and hybridomas which are chemically and structurally identical to those claimed. It is unclear that one of skill in the art could derive a monoclonal antibody and hybridoma identical to those claimed. Undue experimentation would be required to screen all of the possible antibody and hybridoma species to obtain the claimed antibody and hybridoma. Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed antibodies, a suitable deposit of hybridoma cell line producing antibody 3G4 for patent purposes, evidence of public availability of the claimed antibody or evidence of the reproducibility without undue experimentation of the claimed invention, is required.

Since the biological materials are essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. If the biological materials are not so obtainable or available, the requirements of 35 U.S.C. 112 may be satisfied by a deposit of the biological materials.

The specification does not disclose a repeatable process to obtain the biological materials and it is not apparent if the biological materials are readily available to the public. It is noted that Applicant has deposited the biological materials (p. 10 of the specification), but **there is no indication in the specification as to public availability**. If the deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific biological materials have been deposited under the Budapest Treaty and that **the biological materials will be irrevocably and without restriction or condition released to the public upon the issuance of a patent**, would satisfy the deposit requirement made herein.

New Rejection

(necessitated by amendments)

Claim Rejections - 35 USC § 112

4. Claims 1, 14, 18, 23, 51, 52, 94, 96, 97, 98, 99, 132, 133, 135-137, 139-143, and 145-147 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed compositions, hybridomas, and methods comprising an antibody:

(a) wherein the antibody comprises a heavy chain variable region that comprises CDRs SEQ ID NOs:10-12 **and** comprises a light chain variable region that comprises CDRs SEQ ID NOs:13-15; or

(b) wherein the antibody comprises at least two variable regions that each comprise three CDRs wherein at least one of said variable regions is the heavy chain variable region SEQ ID NO:2 and/or the light chain variable region SEQ ID NO:4,

does not reasonably provide enablement for an antibody comprising a heavy chain variable region that comprises CDRs SEQ ID NOs:10-12 **or** comprises a light chain variable region that comprises CDRs SEQ ID NOs:13-15. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state

of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims rejected are broadly drawn to compositions, hybridomas, or methods encompassing an antibody or antigen binding fragment thereof wherein said antibody or fragment thereof comprises at least two variable regions that each comprise three CDRs, wherein only the sequences of three CDRs are known for one light or one heavy chain, and the sequences of the framework or entire heavy or light chain variable regions are undefined.

The specification discloses in FIG. 18A and FIG. 18B, the DNA and amino acid sequences of the complementarity determining regions (CDRs) of the 3G4 antibody: DNA and amino acid sequences for the heavy (FIG. 18A; SEQ ID NO:1 and SEQ ID NO:2) and light (FIG. 18B; SEQ ID NO:3 and SEQ ID NO:4) chains. The specification discloses anti-tumor effects of antibody 3G4 for mice bearing tumors (Figs 6-8). The specification discloses that antibody 3G4 or human chimeric 3G4 (ch3G4) can enhance the survival of mice infected with murine CMV (p. 308, lines 1-7; Example XXI, p. 315). The specification discloses screening methods to produce antibodies that bind to an aminophospholipid such as phosphatidylserine (section D2, p. 82 through section E1, p. 94).

The state of the prior art is such that it is well established in the art that the formation of an intact antigen-binding site of antibodies routinely requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the

majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, 3rd Edition, 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA, 79(6):1979-1983, March 1982). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Colman P. M. (Research in Immunology, 145:33-36, 1994) teaches that even a very conservative substitution may abolish binding or may have very little effect on the binding affinity (see pg. 35, top of left column and pg. 33, right column). Additionally, Bendig M. M. (Methods: A Companion to Methods in Enzymology, 1995; 8:83-93) reviews that the general strategy for "humanizing" antibodies involves the substitution of all six CDRs from a rodent antibody that binds an antigen of interest, and that all six CDRs are involved in antigen binding (see entire

document, but especially Figures 1-3). Similarly, the skilled artisan recognized a "chimeric" antibody to be an antibody in which both the heavy chain variable region (which comprises the three heavy chain CDRs) and the light chain variable region (which comprises the three light chain CDRs) of a rodent antibody are recombined with constant region sequences from a human antibody of a desired isotype (see entire document, but especially Figures 1-3). While there are some publications, which acknowledge that CDR3 is important, the conformations of other CDRs as well as framework residues influence binding. MacCallum et al (J. Mol. Biol., 262, 732-745, 1996) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col.) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.). The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset et al (Biochemical and Biophysical Research Communications, 307:198-205, 2003, IDS), which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset et al also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (see page 202, left

col.). Thus, the state of the art recognized that it would be highly unpredictable that a specific binding member comprising an antibody variable region but comprising less than all six CDRs of a parental antibody with a desired specificity would retain the antigen-binding function of the parental antibody. Thus, the minimal structure which the skilled artisan would consider predictive of the function of binding and treating cancer or viral infections includes six CDRs (three from the heavy chain variable region and three from the light chain variable region) from parental antibody 3G4 in the context of framework sequences which maintain their correct spatial orientation have the requisite 3G4 binding function. One of ordinary skill in the art could not predictably extrapolate the teachings in the specification, limited to antibodies that comprise the full heavy chain variable region and/or the full light chain variable region of antibody 3G4 (i.e., SEQ ID NOs:2 and 4), or all six CDRs (i.e., SEQ ID Nos:10-15) of monoclonal antibody 3G4.

The specification does not enable the broad antibody genus because where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one particular species, what other species will work. See MPEP 2164.03.

One of skill in the art would neither expect nor predict the appropriate functioning of the antibodies as broadly as is claimed.

Additionally, the art teaches that antibody 3G4 and antibodies previously thought to bind aminophospholipids actually bind lipid-bound serum or plasma proteins. Bevers et al (Clinical Immunology, 2004, 112:150-160) teach that the most frequently occurring antigens are the lipid-bound plasma proteins β_2-glycoprotein I (β_2GPI) and prothrombin (PT), although several other lipid-bound plasma proteins have been reported as antigens for antiphospholipid antibodies (abstract). Both proteins bind to anionic phospholipids, mainly PS, which becomes exposed at the surface of activated platelets, apoptotic cells, or cell-derived microparticles (abstract). Bevers et al teach that the term 'antiphospholipid antibody' is a misnomer and the term 'anti-lipid-bound β_2GPI' antibody or 'anti-lipid-bound-PT' antibody would be more appropriate (p. 150, col. 2 last paragraph bridging to p. 151). Bevers et al teach that several studies demonstrate that binding of β_2GPI to a phospholipids surface is accompanied by a conformational change, which could result in the exposure of cryptic epitopes (p. 152, col. 2). Figures 1 and 3 of Bevers et al illustrate that antibodies actually bind to β_2GPI or PT, wherein antibodies frequently bind more than one lipid-bound β_2GPI or PT. High lateral mobility of a monovalent lipid-bound anti- β_2GPI- β_2GPI complex allows this complex to engage another lipid-bound β_2GPI molecule to form a trimolecular complex (p. 153, col. 1; Fig 1A). Anti-PT antibodies may even be directed to a combined lipid-protein epitope or to neo-epitopes that may arise from conformational changes in membrane-bound prothrombin (p. 155, col. 1-2).

Luster et al (J Biological Chemistry, 2006, 281:29863-71, IDS) and Ran et al (Clinical Cancer Research, 2005, 11:1551-1562, IDS) teach that antibody 3G4, the same 3G4 antibody recited the instant claims, requires β_2GPI for binding to PS. Luster et al further teach that dimeric β_2GPI complexes have increased binding for PS, while monomeric β_2GPI binding to PS was negligible. Antibody 3G4 binds to β_2GPI and promotes the formation of β_2GPI dimers, which in turn, have increased avidity for PS (p. 7, col. 1 and 2). Luster et al teach that 3G4 Fab' fragments do not bind endothelial cells with exposed PS, but 3G4 F(ab')$_2$ fragments could bind, indicating that monomeric 3G4 Fab'/ β_2GPI complexes do not bind endothelial cells with exposed PS and that 3G4/β_2GPI binding to PS is dependent on dimeric complexes of β_2GPI (abstract; p. 7, col. 2).

Given it is known that antibody 3G4 does not actually bind aminophospholipids or phosphatidylserine as its antigen, one of skill in the art could not predictably screen for the claimed antibodies comprising only 3 CDRs that would function as claimed using the screening methods as contemplated in the specification, because the specification only provides guidance for screening for antibodies that bind aminophospholipids such as phosphatidylserine. Further, given that Luster et al teach that 3G4 Fab' fragments do not bind endothelial cells with exposed PS, a F(ab') fragment of at least antibody 3G4 would not only fail to bind to PS for the reasons set forth above, it would fail to produce complexes of β_2GPI required for β_2GPI binding to PS, and ultimately fail to function as a pharmaceutical for treating cancer or viral infections as claimed and contemplated. Antibody fragments and derivatives with similar structure to F(ab') fragments would be

unable to promote the formation of β_2GPI dimers and would not predicatbly have increased avidity for PS nor predictably treat cancer or viral infections as claimed and contemplated. A high quantity of experimentation would be require to make and use the broadly claimed antibodies and hybridomas, and a high quantity of experimentation would be required to screen for the claimed antibodies and hybridomas as contemplated in the specification.

Therefore, in view of the state of the art (Paul W. E. and Rudikoff et al, Colman P. M., Bendig M. M., MacCallum et al and Casset et al, Bevers et al, Ran et al, and Luster et al), the high quantity of experimentation necessary for making and using an antibody that will function as claimed and contemplated, the lack of guidance in the specification, and the absence of working examples for antibodies comprising only 3 CDRs from parental antibody 3G4 that would function as claimed and contemplated, it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed.

5. Given that Applicants' arguments and declarations are not drawn to the currently standing grounds of rejection, these arguments are considered moot.

6. It is noted that Applicants already filed terminal disclaimers for copending applications 10/642,119, 10/642,120, 10/642,124, 10/642,060, and 10/642,071, 10/642,058, 10/642,116, 10/642,065, 10/642,099, 10/642,118, 10/642,064, and

10/642,122 with which the instant previous and new claims share overlapping claimed matter.

7. All other rejections recited in the Office Action mailed October 9, 2007 are hereby withdrawn.

8. **Conclusion:** Claims 107, 130, 131, 148, and 149 are allowed. Claims 134, 138, and 144 are objected to. Claims 1, 14, 18, 23, 51, 52, 94, 96-99, 106, 112, 117, 122-129, 132, 133, 135-137, 139-143, and 145-147 are rejected.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA B. GODDARD whose telephone number is (571)272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Laura B Goddard/
Examiner, Art Unit 1642